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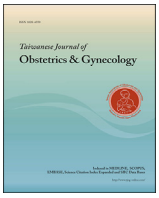

Review Article

Less radical surgery for early-stage cervical cancer: To what extent do we justify it?—Our belief

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ABSTRACT

Cancer of the uterine cervix, following breast cancer, is the second leading cause of death among gynecological cancers in the developed world. Traditionally, surgical management of early-stage cervical carcinoma is considered as a "sterilizing" procedure, since the uterus is removed. Nowadays, because of the postponement of childbearing to an older age, women younger than 45 years old who are diagnosed with early-stage cervical cancer have a strong desire to preserve fertility. Radical trachelectomy (vaginal or abdominal route) is used for fertility preservation in cases of early-stage (International Federation of Gynecology and Obstetrics Stages IA–IB1) cervical carcinomas with remarkable oncological and obstetrical outcomes. However, less radical approaches for ideal candidates may prove safe when fertility preservation is probably feasible.

Introduction

Cancer of the uterine cervix holds the third place among the most common cancers in women worldwide. Approximately 12,360 women with invasive cervical cancer are newly diagnosed each year, and about one-third of them die from this disease [1]. Although the average patient age at diagnosis is 48–50 years, 20–22% of cervical cancer cases are diagnosed in women younger than 39 years [2]. Even in the developed world with organized screening programs for cervical cancer, although cervical cancer is frequently diagnosed at an early stage, the percentage of women suffering from the disease remains high [3].

The International Federation of Gynecology and Obstetrics (FIGO) defines early-stage cervical cancer as FIGO Stage IA–IB1 disease. Currently, for patients with cervical cancer at FIGO Stages IA2–IB1, adequate treatment is based on radical surgery with or without subsequent radiotherapy, depending on the presence of pathologic risk factors such as tumor size, parametrial invasion, lymph node metastasis, positive surgical margins, and deep stromal invasion. However, radical surgery does not spare fertility and the potential of childbearing is eliminated. Therefore, due to the postponement of childbearing to an older age, women younger than 45 years who are diagnosed with cervical carcinoma have a strong desire to preserve fertility [4]. A radical surgery may lead to psychosexual dysfunction, depression, grief, stress, and decreased quality of life. Moreover, significant emotional and physical impacts may be observed [5,6]. Since the number of younger patients who are diagnosed with cancer and plan on a future pregnancy has increased, the gynecological oncology community has recently revised the radical surgical philosophy in order to preserve fertility, maintaining an excellent oncological outcome, without increasing the risk of recurrence.

Less radical surgery for early-stage cervical cancer

Revolutionary treatment for early-stage cervical cancer was first presented in 1994 [7], supporting the concept that the uterine body, and consequently fertility potential, could safely be preserved in well-selected cases. Radical vaginal trachelectomy was later described as removal of cervix, parametrium, and cuff of the vagina with maintenance of the uterine fundus and adnexae. Radical vaginal trachelectomy combined with laparoscopic pelvic lymphadenectomy was considered as the appropriate fertility sparing approach for early-stage cervical cancer.

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Subsequently, abdominal radical trachelectomy was described, as many surgeons were more familiar with this procedure due to its similarities with radical abdominal hysterectomy [8]. However, the abdominal approach results in a wider parametrial dissection than the vaginal route, and it is debatable if this extensive surgery is required for Stage IA2 disease. By contrast, the abdominal procedure could lead to pelvic adhesion formation, which may add to future fertility difficulties. There has been a speculation in the community of obstetricians and gynecologists about the radical treatment of the disease, and over the years the radicality has been abandoned and more conservative techniques have been developed. Initially, there was skepticism about the new procedures; however, the philosophy of conservative surgery has gradually been established, and radical trachelectomy has emerged as a valuable therapeutic method for preserving fertility in young women with early-stage cervical cancer. In recent years, two other methods, laparoscopic and robotic-assisted radical trachelectomy, have been developed. Each procedure has advantages and disadvantages based on the different abilities of the surgeon performing the procedure and the available technical equipment. Up to now, several authors have reported on the safety and efficacy of these two procedures, demonstrating both the obstetrical and the oncological outcomes [9–12].

Multiple studies supported the safety and efficacy of radical trachelectomy [13–15]. In addition, retrospective studies have shown that there is no significant difference in the oncologic outcomes between traditional radical hysterectomy and radical trachelectomy [16]. However, it is almost universally accepted that radical trachelectomy should not be offered to patients with tumors $\geq$ 2 cm in size due to the high rate of relapses (12.5%) [17].

Selection criteria

The current literature supports that conservative management of cervical carcinoma is primarily addressed in women with low-risk early-stage disease. It is of utmost importance to recognize suitable candidates and manage them in an appropriate way.

Most importantly, the strong desire of patients for fertility preservation should be considered, and women who do not wish to preserve their fertility may be excluded. Tumor size is one of the most important factors responsible for recurrence. Lesions larger than 2 cm in size involves a higher risk of recurrence: 12.5% versus 1.2% for lesions < 2 cm in size [17]. The histological type of the cancer should also be taken into account, as squamous cell, adenocarcinoma, and adenosquamous carcinoma are acceptable for radical trachelectomy, while small-cell neuroendocrine carcinoma is not suitable, because it has the worst prognosis due to its association with lymph node metastasis, local/distant relapse, and a need for postoperative chemotherapy.

Radical surgery morbidity

Radical surgery, due to extensive parametrial resection, is accompanied by a high rate of morbidity. Nerve injury, bladder and bowel dysfunction, sexual dysfunction that may appear as dyspareunia, decreased arousal, and decreased swelling are considerably increased.

These problems have a significant impact not only on the sexual life of women, but on their psychology as well, since they lose their interest, are unsatisfied, or suffer from anxiety regarding intercourse [18]. Although the transaction of the uterine arteries poses a high risk for future fertility, there are pregnancies and term births, after uterine artery ligation confirming the successful utero-ovarian circulation [8].

Philosophy of less radical surgery

In recent years, removal of the parametria has been revised due to the morbidity associated with parametrectomy, taking into account the risk factors for recurrence after radical trachelectomy, such as tumor size > 2 cm, positive lymphovascular space involvement (LVSI), and tumor infiltration depth > 10 mm [17]. For patients with tumor size < 2 cm, negative pelvic lymph nodes, and infiltration depth < 10 mm, the risk of parametrial involvement is about 0.6% [19]. Parametrial spread is a strong predictor of recurrence and decreased survival. Parametrial invasion is rare (< 0.4%) in patients with small tumors, no LVSI, and negative pelvic nodes [20]. For the above reasons, radical procedures in patients with a tumor size of < 2 cm are considered as overtreatment. Frumovitz et al [21], in their study of 300 women, found that the rate of parametrial involvement was almost zero.

Our view of early-stage cervical cancer treatment is in agreement with that of the supporters of less radical procedures. We recently supported the fact that less radical surgery is possible in patients with Stage IB1 cervical cancer. Patients with a depth of infiltration of $\leq$ 13 mm and negative lymph nodes represent a subgroup with a very low risk for parametrial spread (< 0.7%). These patients could be considered for less radical surgery such as cervical conization or simple hysterectomy with pelvic lymphadenectomy, in order to minimize morbidity related with radical removal of the cervix and optimize the obstetric outcome. In conclusion, our study confirmed the low incidence of parametrial involvement (< 0.7%) in early-stage cervical cancer—< 2 cm in length, < 13 mm in depth of infiltration, and negative pelvic lymph nodes—as suggested in previous studies [22]. The data compiled from different studies showed a rate of < 1% for parametrial involvement in patients with low-risk characteristics of cervical cancer. These results demonstrate that patients with early-stage cervical cancer are candidates for less radical surgery [23]. Therefore, we identified a group of patients at low risk for parametrial disease who may be candidates for omission of parametrectomy and can be safely cured by a less radical surgery, as already mentioned in the literature.

Neoadjuvant chemotherapy

The role of neoadjuvant chemotherapy (NACHT) in the treatment of early-stage cervical cancer is under investigation. Typical indications for NACHT are to reduce tumor size in order to later facilitate radical surgical resection, as well as minimize prognostic factors that are associated with a poor response such as lymph node metastasis, LVSI, and parametrial involvement, thereby eliminating the need for postoperative adjuvant radiotherapy. Although recent literature describes many different chemotherapeutic regimens and dosages (cisplatin, carboplatin, paclitaxel, mitomycin, vincristine, bleomycin, mitomycin, 5-flouoracil, ifosfamide, etc.), the most commonly used chemotherapy agents are cisplatin (50 g/m^2), vinblastine (1 mg/m^2 on Days 1 and 2), and bleomycin (25 mg/m^2 for 3 days) for two to four cycles. The response to chemotherapy is monitored with magnetic resonance imaging or computed tomography [1,24]. In some patients, there has been no evidence of residual disease in surgical specimens following NACHT. Many authors recommend the use of NACHT prior to the surgery to downstage tumors >2 cm, in order to follow more conservative cervical resection, diminishing the risk of relapse and improving obstetrical results [24]. Nonetheless, the majority of trials found that the role of NACHT in early-stage cervical cancer is not unambiguous, and therefore it should not be used outside of clinical trial protocols. More studies are needed in order to determine the oncological safety of the procedure as well as the obstetrical

outcomes [18]. In a recent review, Pareja et al [1] reported that the pregnancy rate appeared to be higher for patients with tumors ≥ 2 cm in size who underwent NACHT followed by conservative surgery (30.6%), compared with those who underwent immediate Vaginal Radical Trachelectomy (VRT) (24%) or abdominal radical trachelectomy (16.5%).

Sentinel lymph node mapping

Lymph node status reflects parametrial invasion and lymph node metastasis is considered an important prognostic factor for recurrence of cervical cancer, impacting both treatment decisions and patient clinical outcomes. Although complete pelvic lymphadenectomy is obligatory, lymph node status is not included in the classification of staging according to the FIGO. Although approximately 15% of early-stage cervical cancer is complicated with lymph node metastasis and the survival rate for these patients is expected to be adequate since disease response to treatment is satisfactory, apparently a large proportion of patients may undergo an extensive surgery with no direct benefit and be exposed to the potential risk of additional morbidity accompanying a wide lymphadenectomy.

Sentinel lymph node (SLN) mapping as part of the surgical management of selected stage cervical cancer is nowadays recommended in gynecological oncology practices worldwide. An SLN is defined as the first lymph node to which cancer cells are most likely to spread from a primary tumor. Sometimes, there can be more than one SLN. SLN biopsy/ultrastaging is then followed in order to identify the SLN removed and examined to determine possible micrometastasis. A negative SLN biopsy result suggests that cancer has not developed the ability to spread to nearby lymph nodes or other tissues. A positive SLN biopsy result indicates that cancer is present in the SLN and may be present elsewhere. This information may alter postoperative management.

Ongoing prospective trials

Three large prospective trials are currently evaluating the role of more conservative procedures in patients with low-risk early-stage cervical carcinoma. A large multicenter prospective trial (ConCerv) is evaluating the safety and expediency of the conservative approach in women with the disease and appropriate selection characteristics. This trial includes patients with Stage IA2–IB1 disease, with the size of tumor being 2 cm or smaller. Patients who wish to preserve their childbearing ability are treated more conservatively with cone excision and pelvic lymph node dissection including SLN mapping. Women not desiring fertility are treated with simple hysterectomy and pelvic lymphadenectomy [23].

Another large multicenter prospective cohort study (GOG-0278), led by Alan Covens, is designed to evaluate the physical function and quality of life before and after nonradical surgical therapy (extrafascial hysterectomy or cone biopsy with pelvic lymphadenectomy) for Stage IA1 (LVSI+) and IA2–IB1 (≤ 2 cm) cervical cancer [25].

Finally, a randomized trial (Shape trial), led by Marie Plante, compared radical hysterectomy and pelvic node dissection with simple hysterectomy and pelvic node dissection in patients with low-risk early-stage cervical cancer. The recruited population include women with Stage IA2 or IB1 and Grade 1, 2, or 3 disease with squamous or adenocarcinoma histological type and tumor size < 2 cm, and < 10 mm stromal invasion on Loop Electrosurgical Excision Procedure (LEEP)/cone biopsy [26].

Our belief

Up to now, nonradical surgery for the treatment of early-stage cervical cancer seems to be a safe and effective option in well-selected patients. Although cone biopsy alone is commonly applied for Stage IA1 squamous cell carcinoma of the cervix without LVSI, where the risk of pelvic nodal disease is approximately 1% and the recurrence rate is very low, the use of cone biopsy in Stage >IA1 tumors is controversial given the high risk of nodal involvement when depth of infiltration is > 3 mm. Therefore, it is mandatory to consider pelvic lymph node dissection in this group of patients. To this point, many studies [27–39] support the oncological safety of cone biopsy and pelvic lymphadenectomy in Stage ≥ IA2 uterine cervical carcinoma. It is believed that this approach could be considered for young women demanding fertility preservation since obstetrical outcomes may be safer and more effective compared with trachelectomy.

Since lymph node status reflects parametrial invasion, the question that arises is whether we could omit parametrial resection in women with early-stage cervical cancer, tumor size <2 cm, and negative lymph nodes. Given the fact that parametrial tissue may hide microscopic spreading of multifocal disease, we believe that this metastatic disease in the remaining parametrium (after cone biopsy in Stage >IA1 squamous cell carcinoma of the cervix with LVSI) could cause pelvic recurrences if not excluded during surgical exploration. In addition, the risk of pelvic lymph node involvement in Stage IA2 is approximately 8%, while the risk of lymphovascular space invasion is 33% and subsequent recurrence may reach 4%. Therefore, lymphadenectomy should always be considered in these cases. After all, is any possibility for less than less radical surgery without affect the oncological outcome? Multicentric prospective randomized studies are necessary to define the most favorable and appropriate management with regard to both the selection of patients and the appropriate surgical approach. More obstetrical outcomes need to be published based on the number of pregnancies achieved after nonradical treatments.

Conclusively, less radical approaches for ideal candidates may prove safe when fertility preservation is requested. Careful selection of patients remains the hallmark of success.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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